

Synthesis and Cyclization Reaction of *cis,cis*-1,3,5-Triformyl-1,3,5-trimethylcyclohexane

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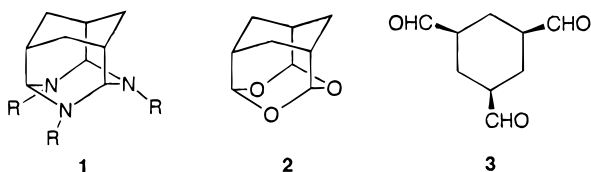
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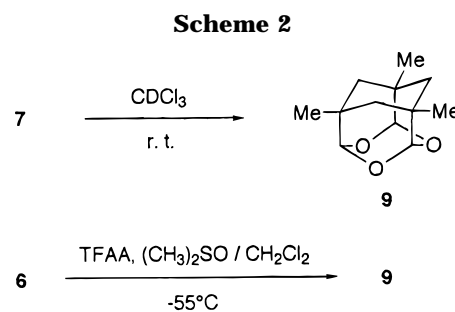
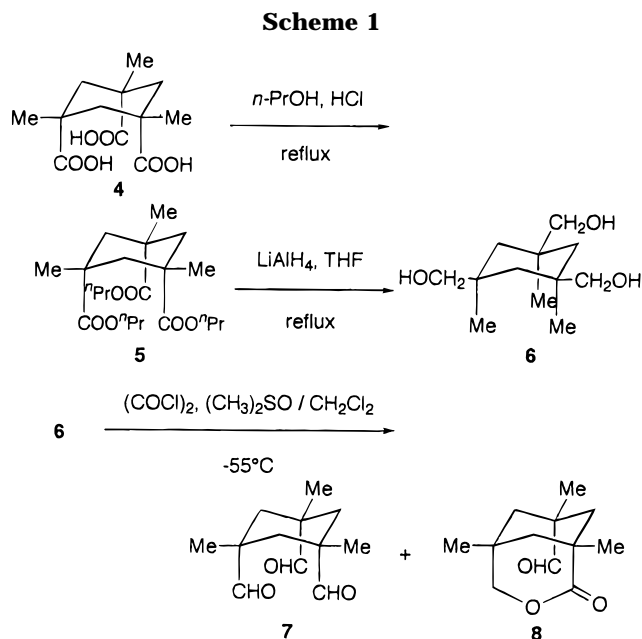
The hydrocarbon wurtzitane (fused boat cyclohexane) has been known since 1974.¹ Nielsen and co-workers prepared the first wurtzitanes incorporating three heteroatoms within the ring. They found the isomerization of triimines to triazawurtzitanes **1**.² However, they also reported that trioxawurtzitane **2** was not obtained from trialdehyde **3**. The contrast between these two reactions



may be explained in terms of their conformations. We introduced methyl groups into the *ipso* positions of **3** and examined the effect of these groups. Here, we report the synthesis of *cis,cis*-1,3,5-triformyl-1,3,5-trimethylcyclohexane (**7**) and the first cyclization of **7** to 1,7,9-trimethyl-3,5,12-trioxawurtzitane (1,7,9-trimethyl-3,5,12-trioxatetracyclo[5.3.1.1^{2,6}.0^{4,9}]dodecane) (**9**). We also present the conformational analysis of **7** and a plausible mechanism for the cyclization of **7** to **9**.

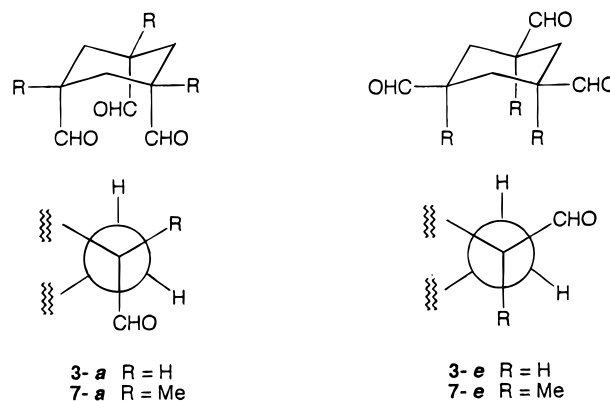
As shown in Scheme 1, **7** was obtained in three steps in an overall yield of 12% from *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid (**4**).³ Esterification of **4** with 1-propanol in excess, by refluxing with hydrogen chloride catalyst, led to triester **5**. Reduction of **5** with lithium aluminum hydride in refluxing THF yielded triol **6** (81% yield from **4**). Mayer and co-workers first prepared triol **6** from methyl ester in 60% yield.⁴ We obtained triol **6** in higher yield from *n*-propyl ester **5** than from the methyl ester.²

A modified Swern oxidation of triol **6** with oxalyl chloride² yielded **7** in 15% yield as well as 5-formyl-*cis,cis*-1,3,5-trimethyl-3-(hydroxymethyl)cyclohexane-1-carboxylic acid lactone (**8**)³ in 14% yield. Trialdehyde **7** is very unstable, and attempts to recrystallize **7** from CH₂Cl₂/hexane led to polymers, which are soluble in hexane. Standing **7** in CDCl₃ at room temperature for 1 day gave trioxawurtzitane **9** in quantitative yield (Scheme 2). Both signals of trioxawurtzitane **9** at 4.85 ppm in the ¹H NMR spectrum and at 97.60 ppm in the ¹³C NMR (DEPT) spectrum indicate that methine protons exist. The IR spectrum of **9** does not show any ν_{CO} band. A



Swern oxidation of triol **6** with TFAA instead of oxalyl chloride also yielded **9** in 23% yield.

As described above, trioxawurtzitane **2** was not obtained from trialdehyde **3**. This conflicting result shows that conformations of these aldehydes play an important role in the cyclization. Trialdehydes **3** and **7** can exist in two chair conformations, respectively; three aldehyde groups are oriented triaxially (**3-a**, **7-a**) or triequatorially (**3-e**, **7-e**). Kemp and co-workers³ studied the conforma-



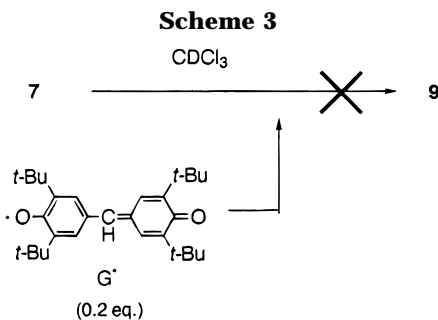
tion of **4** in detail. They ascribed the large chemical shift difference observed between the equatorial and axial methylene proton ($\Delta\delta > 1.2$ ppm) to the triaxial carbonyl groups. The chemical shift difference of **7**, $\Delta\delta = 1.43$ ppm, supports that **7** takes the conformation **7-a**. Furthermore, aldehyde groups of **7-a** are closer to equatorial methylene protons than to axial ones. NOE differential

(1) Cupas, C. A.; Hodakowski, L. *J. Am. Chem. Soc.* **1974**, *96*, 4668.
(2) Nielsen, A. T.; Christian, S. L.; Moore, D. W.; Gilardi, R. D.; George, C. F. *J. Org. Chem.* **1987**, *52*, 1656.
(3) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1981**, *46*, 5140.
(4) Mayer, H. A.; Fawzi, R.; Steimann, M. *Chem. Ber.* **1993**, *126*, 1341.

Table 1. Relative Energies^a for Conformers of Triformylcyclohexanes and Trioxawurtzitanes

structure	rel energy (kcal/mol)
7-e	11.33
7-a	0.00 ^b
9	-11.04
3-e	-1.38
3-a	0.00 ^c
2	-6.85

^a HF/6-31G**. ^b -689.504 945 1 hartree. ^c -572.393 867 2 hartree.



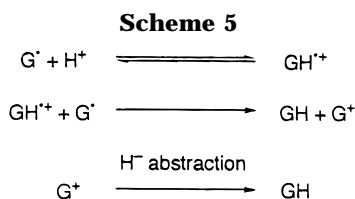
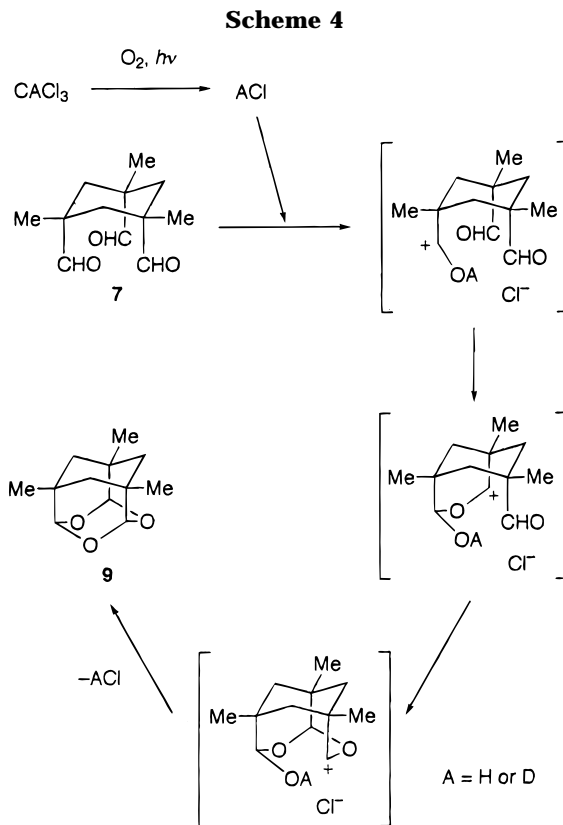
spectra indicate that aldehyde groups of **7** do not correlate with axial methylene protons but with equatorial methylene protons.

The cyclization of trialdehydes to trioxawurtzitanes proceeds with triaxial conformation. The fact that **7** cyclizes and **3** does not suggests that a large difference in the stability of both axial forms exists. We carried out ab initio energy calculations for the conformers of the trialdehydes and the trioxawurtzitanes (Table 1), where all geometries were optimized at the HF/6-31G** level.⁵ The data indicate that the cyclizations of both trialdehydes to trioxawurtzitanes are exothermic. However, a large difference is found for the stability of the conformers of the trialdehydes. The equatorial form is slightly preferable to the axial one for **3**. In contrast with **3**, the axial form of **7** is more stable than the equatorial one. The stability of the axial forms has a great influence on the process that **7** cyclizes and **3** does not.

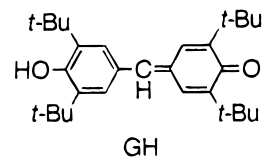
Allowing **7** to stand in CDCl₃ yielded **9** quantitatively, but **7** in acetone-*d*₆ gave decomposition products of **7** very slowly. **7** did not give **9** either in DMSO-*d*₆ or in C₆D₆ at room temperature for 1 day. These results indicate that a catalytic action exists in the cyclization process. The addition of radical scavenger galvinoxyl (G[•])⁶ to a CDCl₃ solution of **7** inhibited the formation of **9** (Scheme 3). But, the reaction of radical initiator 2,2'-azobis(2,4-dimethylvaleronitrile) with **7** in C₆D₆ at 70 °C did not give **9** at all, and heating **7** in C₆D₆ at 70 °C yielded a small amount of **9** with many decomposition products. Furthermore, bubbling hydrogen chloride into the CH₂Cl₂ solution of **7** only gave **9**. Scheme 4 shows a plausible mechanism for the cyclization of **7** to **9** in CDCl₃. It is well-known that chloroform decomposes in the presence of oxygen and light to yield HCl⁷ and that trioxane

(5) Gaussian 94: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.

(6) (a) Adam, W.; Haas, W.; Lohray, B. B. *J. Am. Chem. Soc.* **1991**, *113*, 6202. (b) Kharasch, M. S.; Joshi, B. S. *J. Org. Chem.* **1957**, *22*, 1435. (c) Greene, F. D.; Adam, W. *J. Org. Chem.* **1963**, *28*, 3550.



formation from formaldehyde is acid catalyzed.⁸ This mechanism explains the experimental facts well. The result that the addition of galvinoxyl inhibited the formation of **9** suggests that acids are trapped by galvinoxyl. Coppinger described that galvinoxyl is sensitive to traces of strong acid in hydroxylic or hydrocarbon solvents.⁹ Screttas and co-workers reported the reaction between galvinoxyl G[•] and a series of substituted acetic acids.¹⁰ They found that hydrogalvinoxyl GH was produced and proposed Scheme 5. We confirmed micro



amounts of hydrogalvinoxyl in the first stage (¹H NMR assay). After all hydrogalvinoxyl was lost, 2,6-di-*tert*-butyl-1,4-benzoquinone⁶ and 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde⁶ were mainly produced. The fact that heating **7** in C₆D₆ at 70 °C yielded a small amount of **9**

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(8) (a) Walker, J. F.; Carlisle, P. J. *Chem. Eng. News* **1943**, *21*, 1250. (b) Walling, C.; Augurt, T. A. *J. Am. Chem. Soc.* **1966**, *88*, 4163.

(9) Coppinger, G. M. *J. Am. Chem. Soc.* **1957**, *79*, 501.

(10) Screttas, C. G.; Heropoulos, G. A.; Karayannis, M. I. *Tetrahedron* **1984**, *40*, 5275.

indicates that **7** cyclizes to **9** at 70 °C thermally without catalysts such as HCl.

Experimental Section

General Methods. All reactions were performed in oven-dried glassware equipped with a magnetic stirring bar under argon atmosphere using standard syringe techniques. DMSO and CH₂Cl₂ were distilled from CaH₂ and stored over molecular sieves. All other solvents were of dehydrated grade. Reagents were of commercial grade. ¹H (500 MHz) and ¹³C (125.7 MHz) NMR spectra were recorded in CDCl₃, acetone-*d*₆, C₆D₆, or DMSO-*d*₆.

***cis,cis*-1,3,5-Tris(hydroxymethyl)-1,3,5-trimethylcyclohexane (**6**).**⁴ Hydrogen chloride was bubbled into a suspension of *cis,cis*-1,3,5-trimethyl-1,3,5-cyclohexanetricarboxylic acid (**4**) (6.88 g, 26.6 mmol) in 100 mL of dry 1-propanol for 2 h. The suspension was heated under reflux for 1 h and then cooled to room temperature. Volatiles were removed under reduced pressure, and the residue was treated with 50 mL of ice-water. The oily product was extracted with two 50-mL portions of ether. After being dried with MgSO₄, followed by filtration, the filtrate was concentrated to remove volatiles, leaving 10.86 g of a colorless oil containing *cis,cis*-tri-*n*-propyl 1,3,5-trimethyl-1,3,5-cyclohexanetricarboxylate (**5**) (¹H NMR assay). A solution of the residual oil in THF (35 mL) was then added dropwise to an ice-cooled suspension of lithium aluminum hydride (4.33 g, 114 mmol) in THF (80 mL). After the reaction mixture was refluxed for 20 h and cooled to 0 °C, the salts were decomposed with water/ethanol (10 mL:20 mL). The suspension was filtered, and the solids were extracted with three 30-mL portions of hot ethanol. The solvent was removed under reduced pressure, and the residue was extracted with four 50-mL portions of hot 1,4-dioxane. The extracts were concentrated to 50 mL and cooled to yield **6**⁴ (total yield 4.66 g, 21.5 mmol, 81%). **5**: colorless oil; ¹H NMR (CDCl₃, 500 MHz) δ 0.91 (9H, t, ³J_{HH} = 7.5 Hz, OCH₂-CH₂CH₃), 1.01 (3H, d, ²J_{HH} = 14.6 Hz, CH_aH_b), 1.21 (9H, s, CH₃), 1.63 (6H, sextet, ³J_{HH} = 7.3 Hz, OCH₂CH₂CH₃), 2.73 (3H, d, ²J_{HH} = 14.6 Hz, CH_aH_b), 3.98 (6H, t, ³J_{HH} = 6.7 Hz, OCH₂CH₂CH₃); IR (KBr) ν_{CO} 1740 cm⁻¹; MS (EI) *m/z* 325 (78, M⁺ - OCH₂CH₂-CH₃).

***cis,cis*-1,3,5-Triformyl-1,3,5-trimethylcyclohexane (**7**).** A mixture of dry DMSO (4 mL) and dry CH₂Cl₂ (10 mL) was added to a solution of (COCl)₂ (4.42 g, 34.8 mmol) in 40 mL of dry CH₂Cl₂ at -55 °C. After the mixture was stirred for 30 min, a solution of 1.02 g (4.7 mmol) of **6** in dry CH₂Cl₂ (25 mL)/DMSO (20 mL) was added at -55 °C. The solution was allowed to stand at -55 °C for 2 h. NEt₃ (16 mL) was then added, and the reaction mixture was allowed to warm to 25 °C. Water (50 mL) was then added, and the CH₂Cl₂ layer was separated. Concentrated HCl (3 mL) was added to the aqueous part, followed by extraction with two 50-mL portions of CH₂Cl₂. The combined CH₂Cl₂ solutions were washed once with 50 mL of 1 N HCl and once with 50 mL of an aqueous solution saturated with NaCl. After being dried with MgSO₄ for 30 min, followed by filtration, the filtrate was concentrated to remove volatiles. The residual yellow solid was subjected to a silica gel column and eluted with CH₂Cl₂/acetone (50/1). **7** (0.15 g, 0.71 mmol, 15%) and **8**³ (0.14 g, 0.65 mmol, 14%) were obtained as the first and second fractions, respectively. Attempts to recrystallize **7** from CH₂Cl₂/

hexane led to polymers, which are soluble in hexane and show many complicated broad signals in the ¹H NMR spectrum. **7** was purified by washing with hexane. **7**: colorless solid; ¹H NMR (CDCl₃, 500 MHz) δ 0.98 (3H, d, ²J_{HH} = 14.5 Hz, CH_aH_b), 1.01 (9H, s, CH₃), 2.41 (3H, d, ²J_{HH} = 14.5 Hz, CH_aH_b), 9.35 (3H, s, CHO); ¹³C NMR (CDCl₃, 125.7 MHz) δ 25.62 (CH₃), 38.09 (CCH₂C), 45.98 [(CH₂)₂CCH₃], 202.84 (CHO); IR (KBr) ν_{CO} 1730 cm⁻¹; MS (EI) *m/z* 210 (13, M⁺), 182 (17, M⁺ - CO); HRMS calcd for C₁₂H₁₈O₃ 210.1256, found 210.1287.

1,7,9-Trimethyl-3,5,12-trioxawurtzitane (1,7,9-Trimethyl-3,5,12-trioxatetracyclo[5.3.1.1^{2,6}.0^{4,9}]9**).** The same manner that was employed in the preparation of **7** was used with TFAA instead of (COCl)₂ to yield **9**. Trioxawurtzitane **9** (0.22 g, 1.1 mmol, 23%) was obtained from **6** (1.02 g, 4.7 mmol). **9** sublimes at 90 °C under atmospheric pressure. **9**: colorless crystals; ¹H NMR (CDCl₃, 500 MHz) δ 0.85 (3H, d, ²J_{HH} = 12.2 Hz, CH_aH_b), 1.04 (9H, s, CH₃), 1.34 (3H, d, ²J_{HH} = 12.2 Hz, CH_aH_b), 4.85 (3H, s, OCHO); ¹³C NMR (CDCl₃, 125.7 MHz) δ 27.86 (CH₃), 35.12 [(CH₂)₂CCH₃], 41.59 (CCH₂C), 97.60 (OCHO); MS (EI) *m/z* 210 (41, M⁺); HRMS calcd for C₁₂H₁₈O₃ 210.1256, found 210.1244.

Cyclization of **7 to **9**.** Trialdehyde **7** (2 mg, 0.01 mmol) was added to CDCl₃ (0.6 mL) in an NMR tube. Allowing the solution to stand at room temperature for 1 day gave trioxawurtzitane **9** in quantitative yield (¹H NMR assay).

Trialdehyde **7** (4.5 mg, 0.02 mmol) was added to a solution of galvinoxyl⁶ (2 mg, 0.004 mmol) in CDCl₃ (0.6 mL). After the solution was allowed to stand at room temperature for 40 h, the ¹H NMR signals of **7** did not change.

Trialdehyde **7** (3 mg, 0.01 mmol) was added to a solution of 2,2'-azobis(2,4-dimethylvaleronitrile) (5 mg, 0.02 mmol) in C₆D₆ (0.6 mL). Heating the solution at 70 °C for 1 day did not give **9** at all (¹H NMR assay). Heating **7** (3 mg, 0.01 mmol) in C₆D₆ (0.6 mL) at 70 °C for 1 day yielded a small amount of **9** with many other decomposition products.

Hydrogen chloride was bubbled into a solution of **7** (15.6 mg, 0.074 mmol) in CH₂Cl₂ (10 mL) for 2 h. After the mixture was stirred at room temperature for 1 day, volatiles were removed under reduced pressure. **9** (7.6 mg, 0.036 mmol) was yielded in 50% yield, and other products were not confirmed.

Computational Methods. All geometry optimizations and conformer searches were performed using the Gaussian 94 program.⁵

Acknowledgment. The present calculations were carried out using the Research Information Processing System of the Agency of Industrial Science and Technology (Ministry of International Trade and Industry).

Supporting Information Available: ¹H NMR and ¹³C NMR spectra of compounds **7** and **9**, the spectral changes upon the cyclization of **7** to **9** and upon the addition of galvinoxyl to the solution of **7**, and NOE differential spectra of **7** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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